UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/451,939	12/01/99	MIAO	N CIBT-P02-044

028120
ROPES & GRAY
ONE INTERNATIONAL PLACE
BOSTON MA 02110-2624

HM22/0717

EXAMINER	
BRANNOCK, M	
ART UNIT	PAPER NUMBER
1646	12

DATE MAILED: 07/17/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/451,939	Miao, et al.
Examiner	**Art Unit**
Michael Brannock, Ph.D.	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 30, 2001*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-48* is/are pending in the applica

4a) Of the above, claim(s) *13-15, 17-21, and 23-48* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-12, 16, and 22* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☒ Other: *Correted Raw Sequence Listing*

DETAILED ACTION

Claims 1-48 are pending

Claims 13-15, 17-21 and 23-48 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10, 5/8/01. Further, Applicant is reminded that claims 1-12, 16 and 22 will be examined only to the extent that the claims read on the invention of elected Group II , i.e. *in vivo* administration of the elected species: small molecule agonists or antagonist of patched that are not Protein Kinase A inhibitors.

The traversal is on the grounds that a search of Groups I-II would not be a serious burden on the examiner, e.g. that all of the groups are encompassed within the scope f generic claims present in the application and that a search of all of these groups would be required in order to properly examine such generic claims. This is not found persuasive for the following reasons:

Under MPEP § 803, there are two criteria for a proper requirement for restriction between patentably distinct inventions:

(A) The inventions must be independent (see MPEP § 8702.01, 806.04, 808.01) **or** distinct as claimed (see MPEP § 806.05- §806.05(I)): and

(B) There must be a serious burden on the examiner if restriction is required (see MPEP § 803.02, § 806.04(a)- 806.04(I), § 808.01(a), and § 808.02).

Consistent with current patent practice, a serious search burden may be established by (A) separate classification thereof: (B) a separate status in the art when they are classifiable together: (C) a different field of search. These criteria were met in the above restriction. Further, a search is directed not only to art which would be anticipatory, but also to art that would render the invention obvious. In the instant case, although a search of the *in vitro* methods of Group I overlap a search of the *in vivo* methods of Group II a search of the *in vitro* methods could not be relied upon to provide art that might render obvious the methods of *in vivo* treatment, nor could a search of *in vivo* methods be relied on to provide art that might render the in vitro methods obvious. The methods of Group I- III require different starting materials and different modes of administration, thus three searches would not be coextensive. Further, in many instances, a protein will have been known in the art before the DNA has been discovered that encodes the protein. Often the protein will be known by a name different than the name given the protein after the cloning of the nucleic acid - and may even be associated with a completely different activity than that ascribed to it when the nucleic acid was cloned. Additionally, a small molecule may be well known in the art and the use of such may be well known long before it is realized that the small molecule is an antagonist of a certain protein. Thus a search of the methods of group III could not be replied upon to provide art that may anticipate the claims of Groups I and II, nor *visa versa*. Thus, Groups I, II and III require divergent searches, and to search all inventions would be burdensome. Therefore, the restriction is maintained and made final.

Formal Matters:

Applicant is notified that minor errors in the computer readable form of the sequence listing have been corrected by STIC Systems Branch, see attached page 1 of the raw sequence listing. No action is required on the part of Applicant.

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 5-12 and 22 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a credible asserted utility or a well-established utility. Claims 5 and 6 directed to directed to methods of preventing Parkinson's disease or Huntington's disease. However the term "preventing", given its broadest reasonable interpretation with the specification, requires that absolutely no manifestation of the disease occur. There is no evidence, either in the specification nor in the prior art, that any method to date can accomplish this goal. The specification presents the results of several experiments demonstrating that the hedgehog polypeptides are trophic for embryonic dopaminergic neurons, however there is no support for the absolute prevention of disease, required by the claims, and neither can such support be obtained through reasonable extrapolation of the data.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-12, 16, 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims require a "ptc therapeutic". The specification defines "ptc therapeutic" as that which mimics the effect of naturally occurring hedgehog proteins on patched signaling (see page 11). The specification further appears to define "ptc therapeutic" as a molecule which "binds to patched and alters its signal transduction activity , or compounds which alter the binding and/or activity of a protein (e.g., intracellular) involved in patched signal pathway, and compounds which alter the level of expression of a hedgehog protein, a patched protein or a protein involved in the intracellular signal transduction pathway of patched (see page 48, lines 13-19). Thus, "ptc therapeutic" appears to encompass any and all compounds that alter the activity of patched. However, it is well appreciated that the activities of patched are extremely complex and as yet controversial and incompletely identified (see Stull and Iacovitti, Experimental Neurobiology 169(1)36-43, 2001, especially page 40), therefore the phrase "ptc therapeutic" renders the claims indefinite because those skilled in the art would have to identify the activities of patched in order to determine whether a compound alters these activities.

The claims require methods of promoting survival of neurons or treating a disorder comprising administering a trophic amount of a "ptc therapeutic" or a therapeutically effective amount a "ptc therapeutic", yet the claims fail to require that amount be "trophic" or "therapeutically effective" at any particular thing. For instance, claim 1 encompasses a method for treating survival of substantia nigra neurons in an adult with an amount of a ptc therapeutic that may be trophic only for neurons in the embryo. Thus, it is unclear what the "ptc therapeutic" is trophic or therapeutically effective for. Therefore, the metes and bounds of the claims cannot be determined.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-12, 16, and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of promoting the survival of Dopamine and GABA neurons *in vitro* or in embryonic tissue explants comprising contacting the neurons with sonic hedgehog, does not reasonably provide enablement for *in vivo* methods of promoting the survival of dopaminergic or GABAergic cells comprising the administration of a small molecule agonist or antagonist of patched that is not Protein Kinase a inhibitor nor treatment of diseases in the adult animal with any ptc therapeutic. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification indicates that the survival of Dopamine and GABA neurons in embryonic tissue explants can be promoted with sonic hedgehog (see pages 65-76), however the specification has not provided that adult neurons can be treated similarly. Further, the claims require *in vivo* methods of promoting the survival of dopaminergic or GABAergic cells comprising the administration of a small molecule agonist or antagonist of patched that is not Protein Kinase A inhibitor. As set forth above, the claims appear to encompass the administration of compounds which alter any aspect of patched signaling but are not Protein Kinase A inhibitors. However, there appears to be no disclosure of such a molecule, nor guidance as to how to produce such a molecule, nor is such a molecule known in the art. The claims claim a process using such a molecule, yet the specification appears to offer no guidance other than an invitation to the skilled artisan to perform random trial and error experimentation to try to find such a molecule (see page 48-49 for example), if such a molecule can be found. Further, the art is equivocal about the role of patched signaling pathways in the development of neural tissue. *Hynes et al. Neuron* 15(1)35-44, 1995, found that activation of PKA antagonized the effect of patched activity (see the Abstract), however the picture is appears to be more complex, as the results of *Stull and Iacovitti, Experimental Neurobiology* 169(1)36-43, 2001 suggest that sonic hedgehog does not signal through either PKA, IP-3K/PKC or DA signal transduction pathways (see page 40 first paragraph) and that activation of PKA does not inhibit

sonic hedgehog induction of dopamine neurons (see page 40, 2nd col. 1st paragraph) - a result contradictory to that reported by *Hynes et al.*, and the instant specification. Therefore, due to the lack of direction/guidance presented in the specification regarding which structural features are required of a molecule in order to provide activity, the absence of working examples directed to same, the complex nature of the invention and contradictory state of the prior art (see *Stull and Iacovitti* above), and the state of the prior art which does not appear to embrace such a molecule, undue experimentation would be required of the skilled artisan to make the claimed invention.

7. Claims 1-12, 16 and 22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims require *in vivo* methods of promoting the survival of dopaminergic or GABAergic cells comprising the administration of a small molecule agonist or antagonist of patched that is not Protein Kinase a inhibitor, such molecule being one that alters the activity of a patched signaling pathway, as defined in the specification as a "ptc therapeutic" at pages 11 and 48. However, there appears to be no description of such a molecule, nor guidance as to what structural characteristics such a molecule might possess, nor is such a molecule known in the art.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by *Hynes et al. Neuron* 15(1)35-44, 1995.

Hynes et al. disclose a method of promoting the survival of midbrain neurons, e.g. substantia nigra dopaminergic and GABAnergic neurons comprising contacting the cells with a trophic amount of sonic hedge-hog protein, i.e. a ptc-therapeutic (see the Abstract).

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

MB

July 16, 2001

Attachment for PTO-948 (Rev. 03/01, or earlier)
6/18/01

The below text replaces the pre-printed text under the heading, "Information on How to Effect Drawing Changes," on the back of the PTO-948 (Rev. 03/01, or earlier) form.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the Notice of Allowability. Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136(a) or (b) for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a).

Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.